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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,664	02/03/2006	Gisela G Chiang	13751-036US1/A167 US	7404
26168 7590 01/15/2010				
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EXAMINER				
YU, MISOOK				
ART UNIT		PAPER NUMBER		
1642				
NOTIFICATION DATE		DELIVERY MODE		
01/15/2010		ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

### Office Action Summary

**Application No.**

10/519,664

**Applicant(s)**

CHIANG ET AL.

**Examiner**

MISOOK YU

**Art Unit**

1642

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 17 December 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1, 6-11, 14-16, 18 and 20-38 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 6-11, 14-16, 18 and 20-38 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

The finality of the Office action mailed on 06/30/2009 is withdrawn because Lundstrom, K, 1997, Current Opinion in Biotechnology, vol. 8, pages 578-582 teaches alphaviral vector used in Mastrangelo (2000) of record is used for transient expression, therefore, Mastrangelo (2000) does not anticipate the claimed invention, i.e. CHO cells stably transfected with Bcl-XL and also stably transfected with a vector expressing a protein.

The rejection of record set forth in the previous Office action not repeated here is withdrawn in view of the new rejection below.

#### ***The Following are New Grounds of Rejections***

##### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6-11, 14-16, 18 and 20-38 are rejected under 35 U.S.C. 102(e) as being anticipated by US 20030219871 A1 (the effective filing date of April 02, 2002 to US 60369307)..

US 20030219871 teaches as follows:

[0014] In the present invention strategies are provided to further improve the survival of production cell lines grown constantly in suspension in serum-free medium. The

strategies are based on engineering host cells in order to improve the intracellular-level of anti-apoptotic acting polypeptides. It has been surprisingly found, that the level of intracellular anti-apoptotic acting genes can substantially improve cell viability without showing any negative effect on cell productivity.

[0092] "Transfection" of eukaryotic host cells with a polynucleotide or expression vector, resulting in genetically modified cells or transgenic cells, can be performed by any method well known in the art and described, e.g., in Sambrook et al., 1989 or Ausubel et al., 1987 (updated). Transfection methods include but are not limited to liposome-mediated transfection, calcium phosphate co-precipitation, electroporation, polycation (such as DEAE-dextran)-mediated transfection, protoplast fusion, viral infections and microinjection. Preferably, the transfection is a stable transfection. The transfection method that provides optimal transfection frequency and expression of the heterologous genes in the particular host cell line and type is favored. Suitable methods can be determined by routine procedures. For stable transfectants the constructs are either integrated into the host cell's genome or an artificial chromosome/mini-chromosome or located episomally so as to be stably maintained within the host cell.

[0095] In accordance with the teachings herein, the present invention provides also a method for the expression of an anti-apoptosis gene, a selectable amplifiable marker gene and at least one gene of interest in a host cell. Said method comprising the steps: (i.) introducing into a host cell population, preferably into a hamster host cell population, the nucleic acid sequences that encode for an anti-apoptosis gene, a selectable amplifiable marker gene, and at least one gene of interest, wherein said genes are operatively linked to at least one regulatory sequence allowing for expression of said genes, and (ii.) cultivating said host cell population under conditions wherein said genes are expressed. Methods, teaching to a skilled person in the art how to introduce one or more polynucleotides into a host cell are exemplary described above. Moreover, examples are also given by the invention how one or more genes can be linked with at least one regulatory sequence allowing for expression of said genes. Moreover, it is also described that is preferred to place at least the anti-apoptosis and the selectable amplifiable marker gene in close spatial proximity to allow for a more effective amplification of the anti-apoptosis gene. Host cells, suitable for expressing said genes are those mentioned by the invention. Suitable candidates of an anti-apoptosis gene are listed under Table 2. Preferred is the expression of any of the sequences encoding BCL-xL or BCL-2, more preferred any sequence encoding BCL-xL, even more preferred any BCL-xL encoding sequence of human or hamster origin. In a further preferred embodiment of that method, co-expressing host cells include any of the sequences encoding for any one of the selectable amplifiable marker listed in Table 3. Even more preferred is a method, wherein the host cells comprise a sequence encoding for a heterologous BCL-xL and also sequences encoding for any one of the selectable amplifiable marker listed in Table 3. Most preferred is a method, where the host cell

comprises the sequences encoding for a heterologous BCL-xL and DHFR, especially if the Bcl-xL encoding sequence is of human or hamster origin.

[0096] Methods provided by the present invention allows a person skilled in the art to generate new host cells, particularly for production purposes, showing enhanced cell survival attributed to an delayed or inhibited programmed cell death. Beneficial strategies have been found that dramatically increase viability and productivity of cells, constantly grown in suspension and especially in serum free-medium. Cells according to this invention are highly suitable for the production of several desired polypeptides. The genetically modified host cells described herein not only encode for the genes that are responsible for the enhanced cell survival, e.g. an anti-apoptosis gene and an amplifiable selectable marker gene, but optionally for any gene of interest encoding for a desired peptide. Accordingly, the present invention also provides to persons skilled in the art a process for producing a protein of interest in a host cell, comprising (i.) cultivating any host cells of this invention under conditions which are favorable for the expression of the anti-apoptosis gene and the gene(s) of interest, and (ii.) isolating the protein of interest from the cells and/or the cell culture supernatant. Also provided is the use of said cells for the production of at least one desired protein encoded by a gene of interest.

[0097] Desired proteins are those mentioned above. Especially, desired proteins/polypeptides are for example, but not limited to insulin, insulin-like growth factor, hGH, tPA, cytokines, such as interleukines (IL), e.g. IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, interferon (IFN) alpha, IFN beta, IFN gamma, IFN omega or IFN tau, tumor necrosis factor (TNF), such as TNF alpha and TNF beta, TNF gamma, TRAIL; G-CSF, GM-CSF, M-CSF, MCP-1 and VEGF. Also included is the production of erythropoietin or any other hormone growth factors. The method according to the invention can also be advantageously used for production of antibodies or fragments thereof. Such fragments include e.g. Fab fragments (Fragment antigen-binding=Fab). Fab fragments consist of the variable regions of both chains which are held together by the adjacent constant region. These may be formed by protease digestion, e.g. with papain, from conventional antibodies, but similar Fab fragments may also be produced in the mean time by genetic engineering. Further antibody fragments include F(ab')<sub>2</sub> fragments, which may be prepared by proteolytic cleaving with pepsin.

[0098] Using genetic engineering methods it is possible to produce shortened antibody fragments which consist only of the variable regions of the heavy (VH) and of the light chain (VL). These are referred to as Fv fragments (Fragment variable=fragment of the variable part). Since these Fv-fragments lack the covalent bonding of the two chains by the cysteines of the constant chains, the Fv fragments are often stabilised. It is advantageous to link the variable regions of the heavy and of the light chain by a short peptide fragment, e.g. of 10 to 30 amino acids,

preferably 15 amino acids. In this way a single peptide strand is obtained consisting of VH and VL, linked by a peptide linker. An antibody protein of this kind is known as a single-chain-Fv (scFv). Examples of scFv-antibody proteins of this kind known from the prior art are described in Huston et al. (1988, PNAS 16: 5879-5883).

Also note the claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 6-11, 14-16, 18 and 20-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim and Lee (IDS filed on 10/22/2007, Biotechnology and Bioengineering, vol. 71, 2000/2001) in view of Mastrangelo (2000), IDS filed on 10/22/2007, Biotechnology and Bioengineering, vol. 67, pages 555-564.

The difference between the Cho cells taught by Kim and Lee (IDS filed on 10/22/2007, Biotechnology and Bioengineering, vol. 71, 2000/2001) and the instantly claimed invention is that the Cho cells taught by Kim and Lee is stably transfected with Bcl-2, not Bcl-XL.

Mastrangelo et al teaches that the over expression of bcl-2 family members enhances survival of mammalian cells in response to various culture conditions. The cited art specifically teaches genetically engineered BHK-bcl-xL and CHO-bcl-xL cells which were cloned under selection pressure (page 545, creation of stable transfectants, page 547, col.1 para. 4). The cited art further teaches production of recombinant protein

of interest (CAT and IL-12) in the genetically engineered CHO and BJK cell lines that express anti-apoptotic bcl-xL gene (page 546 col.2 para. 3, page 547, col.1 para.2, page 549, fig-5, page 550, fig-8, page 551, fig-11, page 552, fig-12). The cited art further teaches that cellular life spans were doubled in both BHK-bcl2 and CHO-bclx(L) cells relative to the parental cell lines. Furthermore, the presence of these gene products provided increases of up to 2-fold in recombinant CAT production. Similarly over expression of bcl-2 and bcl-x(L) genes also increases IL-12 production in the CHO and BHK cells. The cited art clearly establishes that the over expression of bcl-2 family member genes can have a significant impact on culture viabilities and recombinant protein production in mammalian cells (see page 544, abstract).

Thus it would have been obvious to one ordinary skilled in the art at the time the instant invention was made to modify Kim and Lee by substituting Bcl-XL taught by Mastrangelo et al., instead of Bcl-2. One would have been motivated to do so since Mastrangelo et al., teaches that "even during such harsh treatment, Bcl-XL was able to enhance the survival of both cultures, providing CHO cells with viable numbers that were nearly 20-fold that of the controls after five days of exposure". Note abstract of Mastrangelo et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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